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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,600	04/01/2002	Alain Aulombard	IVD 1127	6447
27546	7590	06/24/2004	EXAMINER	
SANOFI-SYNTHELABO INC. 9 GREAT VALLEY PARKWAY P.O. BOX 3026 MALVERN, PA 19355			ANDERSON, REBECCA L	
			ART UNIT	PAPER NUMBER
			1626	

DATE MAILED: 06/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/030,600

Applicant(s)

AULOMBARD ET AL.

Examiner

Rebecca L Anderson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 May 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 16-18 and 31 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 17, 18 and 31 is/are rejected.
- 7) ☒ Claim(s) 1 and 16 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 16-18 and 31 are currently pending in the instant application. Claims 1 and 16 appear allowable over the prior art of record. The rejections of claims 17, 18 and 31 are maintained.

Response to Amendment and Arguments

The amendments and arguments filed 3 May 2004 have been entered into the application. Applicant has cancelled claims 2-15, 19-30 and 32-24. Claims 1, 16 and 31 have been amended to include only the elected subject matter. The amendments to claims 1 and 16 have overcome the objection of these claims.

In regards to the 35 USC 103(a) rejections of claims 17, 18 and 31 applicant argues that the compounds of examples 68-70 of U.S. patent No. 5,780, 466 are not prepared by the resolution of 2-(3,4-dichlorophenyl)-2-(2-hydroxyethyl)morpholine or any other 2-hydroxyethyl morpholine derivative of the formula II with an optically active acid as has been suggested by the Examiner but are prepared by resolution of a compound of the formula XXVII. Furthermore, applicant argues that although the disclosure of US Patent No 5,780,466 concerns the compounds of the formula II in an enantiomerically pure form or in a racemic form, nowhere in the extensive disclosure of the patent is there any specific disclosure concerning the actual resolution of a compound of the formula II or the use of such a compound as an intermediate to prepare enantiomerically pure tachykinin receptor antagonist compounds. These arguments are not found persuasive since the instant claims are drawn to applicants instant compound of the formula I in an enantiomerically pure form with an optically

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active organic acid and since the prior art reference does disclose the compounds of the formula (II), specifically the compounds of the formula II as found in preparations 1.5 and 1.11 which are racemic mixtures of the applicants instantly claimed compound, and since the prior art discloses on column 23, lines 30-37 that the enantiomers of the compounds of the formula (II) are included in the invention and since column 47, lines 34-43 disclose that the compounds of the formula (II) wherein A is $-O-CH_2-CH_2$ and E is H can be resolved into the specific enantiomers by resolving with an optically active acid, for example with (+) or (-) tartaric acid by known methods, this disclosure, of which, therefore renders obvious applicants instantly claimed compounds.

Applicant also argues that US Patent No. 5,780,466 actually teaches away from the use of compounds of the formula I as intermediates since they are obtained in very low yields of 1 and 2 percent. This argument is not found persuasive since the instant claims are not drawn to the methods of use but are drawn to the compounds themselves, which, as described above, are obvious over the disclosure of US Patent NO. 5,780,466.

In regards to the combination rejection applicant argues that US Patent No. 5,616,577 does not cure applicants asserted inadequacy of US Patent No. 5,780,466 since applicants claimed compounds differ significantly structurally from the chiral hydrazines disclosed in US Patent No. 5,616,777 and it is therefore not seen how the use of chiral acids such as L-DTTA and D-DTTA to resolve such structurally different chiral hydrazines could teach the compounds of the instant claims. This argument is not found persuasive since the secondary reference of US Patent NO. 5, 616,577 was

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used to show the common knowledge in the resolution of racemic mixtures with optically active organic acids.

Claim Objections

Claims 1 and 16 are objected to because of the following informalities: Claim 1 contains the word "or" after "with" and before "optically active organic acids". This word should be removed from the claim since it is unnecessary and confusing. Appropriate correction is required.

Maintained Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

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not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,780,466.

Claims 17 and 31 claim an optically active salt of the enantiomerically pure compound of formula (I) wherein X represents a halogen (claim 17), specifically chlorine or fluorine (claim 31), with optically active organic acids.

Determining the scope and contents of the prior art

The prior art of record, US Patent No. 5,780,466 discloses the compounds of formula (II), column 21, line 5, and column 23, lines 30-37 in enantiomerically pure form or in racemic form which are useful in the preparation of the compounds of formula (I), column 2, lines 20-25. The compounds of formula (I) as found in the prior art are useful for therapeutic use in pathological phenomena involving the tachykinin system, such as pain, allergy and inflammation, column 1, lines 14-18. Specific enantiomerically pure compounds of formula (I) of the prior art are found, for example, on columns 116 and 117 in examples 68, 69 and 70. US Patent No. 5,780, 466 discloses the compounds of formula (II) of scheme 3, column 33, line 5 wherein E can be H and A is O-CH₂-CH₂-, of line 15, column 47 wherein A is O-CH₂-CH₂ and E is H, and of preparation 1.5, 2-(3,4-Dichlorophenyl)-2-(2-hydroxyethyl) morpholine, which corresponds to applicants instant compound of formula (I) wherein X is chlorine. Column 47, lines 34-43 discloses

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that to resolve an intermediate of formula (II) one forms a salt with an optically active acid, for example with (+) or (-) tartaric acid.

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art of record and the instantly claimed invention is that the prior art does not specifically disclose the optically active salt of the enantiomerically pure compound of the formula (I) with an optically active acid as instantly claimed. However, the prior art does disclose the compound of formula (II) as found in applicants instant claims, as formula (I), wherein X is chlorine which can be in the form of an enantiomer or a racemic mixture and can be resolved by formation of a salt with optically active acids, for example with (+) or (-) tartaric acid and discloses the compound of formula (I) in its enantiomerically pure forms, for example, examples 68, 69 and 70, columns 116 and 117

Resolving the level of ordinary skill in the pertinent art

Minus a showing of unobvious results, it would have been obvious to one of ordinary skill in the art at the time of the invention to prepare an optically active salt of the enantiomerically pure compound of formula (I) wherein X represents a halogen, specifically chlorine, as instantly claimed when faced with the prior art of US Patent No. 5,780,466 which discloses enantiomerically pure compounds of the formula (I), such as those of examples 68-70, and discloses the intermediate compound of formula (II), specifically 2-(3,4-Dichlorophenyl)-2-(2-hydroxyethyl) morpholine which can be resolved by formation of a salt with optically active acids, for example, tartaric acid. The motivation would be to prepare enantiomerically pure compounds of the formula (I) of the prior art by preparing enantiomerically pure intermediate compounds of the formula

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(II) which is done by the formation of a salt with an optically active organic acid, in order to have more compounds of the formula (I) which are useful for the treatment of pathological phenomena involving the tachykinin system.

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,780,466 as applied to claims 17 and 31 above, and further in view of US Patent No. 5,616,777. While US Patent No. 5,780,466 discloses or renders obvious optically active salts of the enantiomerically pure compound of formula (I) wherein X is halogen, specifically chlorine or fluorine, with optically active organic acids as instantly claimed, it fails to disclose the specific optically active organic acids of L-(-)- or D-(+)-di-para-toluoyltartaric acid as claimed in claim 18. However, US Patent No. 5,616,777 discloses "chiral acids" which are used to resolve a mixture of diastereomers, with preferences towards L-DTTA (di-p-toluoyl-L-tartaric acid, column 4, line 54) and D-DTTA (di-p-toluoyl-D-tartaric acid, column 4, line 53) (column 5, lines 17-25). Reaction Scheme 1, columns 5 and 6 discloses the use of the "chiral acid" to resolve the diastereomers into salts of the enantiomerically pure compounds with the optically active organic acids or "chiral acids". While US Patent No. 5,616,777 fails to disclose an optically active salt of the enantiomerically pure compound of formula (I) as instantly claimed with an optically active organic acid, it does disclose that L-DTTA and D-DTTA are preferred "chiral acids" which are resolving agents for resolving diastereomers into enantiomerically pure optically active salts with an optically active organic acid.

Therefore, one of ordinary skill in the art, minus a showing of unobvious results, would be motivated to prepare optically active salts of the enantiomerically pure

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compound of formula (I) with L-DTTA or D-DTTA as instantly claimed when faced with the primary reference which discloses that optically active organic acids such as tartaric acid are resolving agents which prepare optically active salts of the enantiomerically pure compound of formula (II) with optically active organic acids and further in view of the secondary reference which discloses that L-DTTA and D-DTTA are optically active organic compounds which are useful for resolving racemic mixtures, i.e. they are the "chiral acids". Especially since US Patent No. 5,616,777 discloses that L-DTTA and D-DTTA are preferred as the resolving acids, i.e. the "chiral acids" The motivation would be to prepare more the enantiomerically pure compounds of the formula (I) as found in US Patent No. 5,770,466, for example, examples 68, 69, 70 etc. which is a useful compound for the treatment of pathological phenomena involving the tachykinin system such as pain, allergy and inflammation (column 1, lines 14-18) by resolving more compounds of the formula (II) as found in US Patent No. 5,780,466 by forming salts with optically active acids, specifically L-DTTA or D-DTTA.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

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extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (571) 272-0696. Mrs. Anderson can normally be reached Monday through Friday 5:30AM to 2:00PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph McKane, can be reached at (571) 272-0699.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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